



ANTARCTICA
 ARGENTINA
 AUSTRALIA
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 UK
 URUGUAY
 USA
 VENEZUELA

Confidential



PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES INC
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

August 3, 2000

DUPLICATE

ORIG AMENDMENT

BC

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urologic
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)
 Amendment to Pending Application: Withdrawal of Alternate
 Diluent Manufactured by Pharma Hameln GmbH

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request from the Division made on July 26, 2000 for withdrawal of the alternate diluent (Sterile Water for Injection, USP, 1 mL ampule) manufactured by ~~Pharma Hameln GmbH~~

Accordingly, on advice from the Agency, we hereby withdraw the alternate diluent manufactured by ~~Pharma Hameln GmbH~~ of the above referenced NDA.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

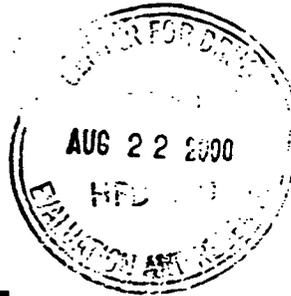
Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at (781) 681-2267, or the undersigned at (781) 681-2298.

Yours sincerely,

Pamela Williamson Joyce
 Vice President,
 Regulatory Affairs

FAX

ORIGINAL



CONFIDENTIAL

Date: 02 August 2000

2

Serono Laboratories, Inc.
 100 Longwater Circle
 Norwell, MA 02061

REVIEWS COMPLETED

DATE

ORIG AMENDMENT
B/M

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149

Phone: (301) 827-4260

Fax phone: (301) 827-4267

CC: _____

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

REMARKS: Urgent For your review Reply ASAP Please comment

Dear Freshnie,

This fax serves as clarification of the annotation of Ovidrel package Insert (Table 8) for Adverse Events from ART studies: 7927, 7648 & 9073, as requested by the Medical Reviewer.

The data found in Table 8 is taken from Table 6 of the 120-day safety update (dated April 7, 2000). Table 6 of the 120-day update shows AE's by Body System for 3 ART studies: 7927, 7648 & 9073. Table 8 of the PI shows additional preferred terms, which are taken from the individual study reports.

- 7927 & 7648 used the WHOART dictionary for AE coding; 9073 used the COSTART dictionary. In order to integrate the data using the same body systems, AE data from 9073 was reclassified to WHOART. (The attached page provides the individual AE's from 9073 and their classifications under the WHOART dictionary).
- **Here's a double-check.** Table 4 of the 120-day safety update shows AE's for 2 ART studies: 7927 & 7648. Table 6 of the 120-day safety update shows AE's for 3 ART studies: 7927, 7648 & 9073. The difference between the 2 tables (Table 4 & Table 6) are 12 Ovidrel patients (38 - 26=12) and 18 Profasi patients (58 - 40=18) who experienced AE's in the 9073 study. As indicated in the first row of Table 25 of the 9073 Study Report (p.78), the total number of patients who experienced any event were 12 in the Ovidrel group and 18 in the Profasi group.

Note that I will also update the electronic annotated PI.

Please call me at (781) 681 2267 if you need further clarification. Sincerely, Debbie

Investigator	Patients Who had Adverse Event Affected		(WHOART Coding System)		Body System	Preferred Term
	ID	Treatment	TNUM	INIT		
BRUISING AROUND INJECTIONS SITE, SUBCUTANEOUS	39	Ovidrel	1	31	Application Site Disorder	INJECTION SITE
BRUISING AROUND SUBCUTANEOUS INJECTION SITE	11	Profasi	1	7	Application Site Disorder	INJECTION SITE
BRUISING AT INTRAMUSCULAR INJECTION SITE	83	Profasi	1	57	Application Site Disorder	INJECTION SITE
MILD BRUISING AROUND INJECTION SITE	13	Ovidrel	1	9	Application Site Disorder	INJECTION SITE
SLIGHT BRUISE WITH IM INJECTION	62	Ovidrel	2	79	Application Site Disorder	INJECTION SITE
PAIN - MILD AROUND INJECTION SITE	8	Profasi	1	22	Application Site Disorder	INJECTION SITE
PAIN (SUBCUTANEOUS SITE)	2	Profasi	1	1	Application Site Disorder	INJECTION SITE
PAIN AFTER SUBCUTANEOUS INJECTION	3	Profasi	1	3	Application Site Disorder	INJECTION SITE
PAIN AROUND INJECTION SITE	15	Ovidrel	1	11	Application Site Disorder	INJECTION SITE
PAIN AROUND INJECTION SITE (SEVERITY MODERATE)	7	Ovidrel	1	4	Application Site Disorder	INJECTION SITE
PAIN AROUND INJECTION SITE-SUBCUTANEOUS SITE	24	Profasi	1	25	Application Site Disorder	INJECTION SITE
PAIN AROUND SUBCUTANEOUS INJECTION SITE	37	Profasi	1	30	Application Site Disorder	INJECTION SITE
PAIN AT INJECTION SITE	54	Profasi	1	49	Application Site Disorder	INJECTION SITE
PAIN AT INJECTION SITE - SUBCUTANEOUS	29	Profasi	1	18	Application Site Disorder	INJECTION SITE
PAIN AT INJECTION SITE INTRAMUSCULAR	28	Ovidrel	1	19	Application Site Disorder	INJECTION SITE
PAIN AT SITE OF SUBCUTANEOUS INJECTION	49	Ovidrel	1	52	Application Site Disorder	INJECTION SITE
PAIN AT SUBCUTANEOUS INJECTION SITE	31	Profasi	1	27	Application Site Disorder	INJECTION SITE
PAIN AT SUBCUTANEOUS INJECTION SITE	41	Ovidrel	1	35	Application Site Disorder	INJECTION SITE
PAIN AT SUBCUTANEOUS INJECTION SITE	55	Profasi	1	53	Application Site Disorder	INJECTION SITE
PAIN AT SUBCUTANEOUS INJECTION SITE	85	Profasi	1	83	Application Site Disorder	INJECTION SITE
PAIN AT THE INJECTION SITE INTRAMUSCULAR	37	Profasi	1	30	Application Site Disorder	INJECTION SITE
PAIN AT TIME OF INJECTION AT INTRAMUSCULAR SITE	21	Ovidrel	1	21	Application Site Disorder	INJECTION SITE
PAIN AT TIME OF INJECTION AT SUBCUTANEOUS SITE	21	Ovidrel	1	21	Application Site Disorder	INJECTION SITE
PAIN EXPERIENCE AT TIME OF INTRAMUSCULAR INJECTION	58	Profasi	1	48	Application Site Disorder	INJECTION SITE
PAIN EXPERIENCE AT TIME OF SUBCUTANEOUS INJECTION	58	Profasi	1	48	Application Site Disorder	INJECTION SITE
PAIN EXPERIENCED AT INJECTION SITE (IMI)	35	Profasi	1	29	Application Site Disorder	INJECTION SITE
PAIN EXPERIENCED AT INJECTION SITE (SUBCUTANEOUS)	35	Profasi	1	29	Application Site Disorder	INJECTION SITE
PAIN WHILE INJECTING AT INTRAMUSCULAR SITE	33	Profasi	1	38	Application Site Disorder	INJECTION SITE
PAIN WHILST SUBCUTANEOUS INJECTION BEING DONE	53	Ovidrel	1	47	Application Site Disorder	INJECTION SITE
PAIN: ADMINISTRATION OF IMI INJECTION & FOLLOWING	85	Profasi	1	83	Application Site Disorder	INJECTION SITE
SLIGHT BURNING IM INJECTION SITE	63	Ovidrel	2	62	Application Site Disorder	INJECTION SITE
STINGING AT INJECTION SITE	54	Profasi	1	49	Application Site Disorder	INJECTION SITE
STINGING SENSATION AT SUBCUTANEOUS INJECTION SITE	82	Ovidrel	1	55	Application Site Disorder	INJECTION SITE
NUMB FEELING AROUND INJECTION SITE-INTRAMUSCULAR	24	Profasi	1	25	Application Site Disorder	INJECTION SITE
REDNESS AROUND INTRAMUSCULAR INJECTION SITE	54	Profasi	1	49	Application Site Disorder	INJECTION SITE
REDNESS AT INJECTION SITE - SUBCUTANEOUS	83	Profasi	1	57	Application Site Disorder	INJECTION SITE
REDNESS AT SUBCUTANEOUS INJ SITE	54	Profasi	1	49	Application Site Disorder	INJECTION SITE
IRRITATION AROUND INJECTION SITE(ITCHING)SUBC.SITE	20	Profasi	1	15	Application Site Disorder	INJECTION SITE
ITCHING AROUND SUBCUTANEOUS INJECTION SITE	30	Profasi	1	23	Application Site Disorder	INJECTION SITE
ITCHING SENSATION AT SUBCUTANEOUS INJECTION SITE	50	Profasi	1	42	Application Site Disorder	INJECTION SITE
TWITCHING IMI (INTRAMUSCULAR SITE)	2	Profasi	1	1	Application Site Disorder	INJECTION SITE

Note: There are 12 unique Ovidrel patients and 18 Profasi patients.

FAX

CONFIDENTIAL

DUPLICATE

Serono

PART OF THE ARL SERONO GROUP

Serono Laboratories, Inc.

100 Longwater Circle

Norwell, MA 02081

ORIG AMENDMENT

AUG 2000
B.M.

Date: 02 August 2000

1

To: Ms. Freshnie DeGuia
(HFD-580)

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

re: Ovidrel NDA 21-149

Phone: (301) 827-4260

Fax phone: (301) 827-4267

CC:

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

REMARKS: Urgent For your review Reply ASAP Please comment

Dear Freshnie,

This fax serves to provide a response to the Medical Reviewers request for clarification of the numbers of patients with OHSS as reported in the Ovidrel 7648 Study Report.

- Section 2 (synopsis) of the 7648 Study Report states that there were 2 patients with OHSS: 1 r-hCG (pt 7-17) and 1 u-hCG (pt 3-31), which were coded as OHSS. Appendix E of the protocol provided the definition of the syndrome. The investigator descriptions were:

7-17: Mild Ovarian Hyperstimulation Syndrome

3-31: OHSS Abdominal Pain

AE's coded as OHSS can be found in section 16.4.36 of the 7648 Study Report.

- 13 patients had symptoms of OHSS, which weren't necessarily coded as AE's. These include the 2 patients above. A detailed listing of the 13 patients (7 r-hCG, 6 u-hCG) who showed any individual symptom of OHSS can be found in section 16.4.35 of the 7648 study report.

se call me at (781) 681 2267 if you need further clarification. Sincerely, Debbie

Dequis

NDA 21-149

Serono Laboratories, Inc.
Attention: Pamela Williamson-Joyce
Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

JUL 31 2000

Dear Ms. Williamson-Joyce:

Please refer to your November 23, 1999 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Ovidrel (choriogonadotropin alfa for injection).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide the following on the characterization/proof of structure of the drug substance:
 - a. Information on the characterization of _____ or a justification as to why it was not characterized.
 - b. The percentage of _____ present in the drug substance.
 - c. Information and data for the preparation and characterization of _____
2. On the methods of manufacture of the drug substance, please provide the following:
 - a. Name and address of supplier, and certificate of analysis for _____
 - b. COA of the following materials: _____
 - c. Information on how the two _____ and _____, were tested before being used for _____
 - d. A detailed explanation for your batch naming system.
3. On the Regulatory Specifications and Analytical Methods of the drug substance, please establish a specification for the absence of _____ in the release specifications of the drug substance.
4. On the stability of the drug substance, please provide the following:
 - a. The missing texts between 2nd and 3rd lines of _____ section in vol. 2.9, pp. 122.
 - b. The _____ HPLC chromatogram provided in vol. 2.9, pp. 141 is for the result of _____

- c. The stability limit for _____ by _____ HPLC should be revised from _____ (Vol. 2.9, p. 119) to NMT _____ as that for the drug substance (vol. 2.9, pp. 29).
 - d. The stability limit for _____ in vol. 2.9, pp. 119) should be revised to read "confirm with the reference standard, and no other bands identified out of the _____"
 - e. A test and specifications for _____ should be established in the stability testing of the drug substance.
5. On the container closure of the drug product, please provide chemistry information for the components of the container/closure system including names and addresses of the suppliers, and certificate of analysis. Alternately, references to relevant DMF(s) with supplier's letter of authorization will suffice.
6. On the stability of drug product, we have the following recommendations:
- a. The sterility test used for stability studies be replaced by a container/closure integrity test to avoid false positive results.
 - b. The substitution of a full bioassay with a bioidentity assay for stability testing (as provided in the stability reports, amendment dated 6-26-00) is not acceptable at this time. Please clarify whether a full bioassay will be used for the post-approval stability testing. It is acceptable to perform the bioassay less frequently for stability.
 - c. Please provide representative _____ HPLC chromatograms for the determination of _____ product at different testing intervals.
 - d. A post approval stability commitment including the number of lots to be tested annually and the action to be taken when a failure of stability testing is discovered should be provided.
7. Please provide method validation results for testing purity using _____ HPLC for the drug product.

If you have any questions, please contact Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/s/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products;
DRUDP (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA21-149

Page 3

Archival NDA 21-149

HFD-580/division file

HFD-580/DeGuia/Rumble/Rhee/Allen/Shames

HFD-510/Wu, Yang

Drafted by: ED/07.28.00

Initialed by: MRhee/YYang07.28.00

Final: EDeGuia07.28.00

INFORMATION REQUEST (IR)

Meeting Minutes

Date: July 25, 2000

Time: 3:00 – 3:30 PM

Location: PKLN; 17B-43

NDA: 21-149

Drug Name: Ovidrel (choriogonadotropin alfa for injection)

Indication: final follicular maturation

Technology (ART)

Assisted Reproductive

Type of Meeting: Status/Labeling Meeting (8-month)

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug-Products (DRUDP; HFD-580)

Daniel Shames, M.D., Acting Deputy Director, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D., Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Duu Gong Wu, Ph.D. - Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products DMEDP, (HFD-510)

Yvonne Yang, Ph.D., Chemistry Reviewer, DMEDP, (HFD-510)

Karen Davis-Bruno, Ph.D. - Pharmacologist, DRUDP (HFD-580)

Ronald Kavanagh, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the Team's review for this pending NDA.

Background: This new NDA was submitted for induction of final follicular maturation and early luteinization in infertile women who have been appropriately pretreated with follicle stimulating hormone as part of an Assisted Reproductive Technology (ART) program such as *in-vitro* fertilization and embryo transfer or

This application is on a 10-month PDUFA review clock and the User Fee goal date is September 24, 2000. not due

Decisions reached:

Clinical:

- review is right on track with the Goal Date
- there is no justification for the 500 mcg dose when the 250 mcg is just as effective; only the lowest effective dose will be considered for approval

- the proposed packaging configuration of two vials of 250 mcg choriogonadotropin alfa and one vial (1 mL) of the diluent is unacceptable (See OPDRA's review dated June 27, 2000); the sponsor will be asked to withdraw the package

Chemistry

- secondary review is being finalized
- some missing information will be requested in a regulatory letter to be sent to the sponsor this week
- clarified with the reviewing Medical Officer that the \pm 10% deliverable dose would not be a clinical concern
- there are some DMF problems with the _____, since this will be used as an alternate diluent only, the sponsor will be asked to withdraw the _____ and keep the _____ as the primary source

Clinical Pharmacology and Biopharmaceutics

- still waiting for consult review from Biometrics regarding gender differences
- review is on track

Pharmacology/Toxicology

- review was completed on April 12, 2000
- additional labeling comments will be incorporated in the draft labeling

Statistics

- review is on-going

Tradename Review

- OPDRA does not object to the use of the proprietary name, Ovidrel

DSI Inspection

- Roy Blay of the Office of Compliance is currently inspecting the foreign sites

Microbiology

- expected date of completion of the review will be early August

Labeling

- initial CMC changes are already incorporated in the draft labeling on the N: drive; any other initial revisions should be made on the label and be sent to the sponsor by early next week

Action Items:

- Information Request (IR) letter regarding chemistry deficiencies should be sent to the sponsor before Friday, July 28, 2000
- initial revisions on the label should be sent to Serono by early next week
- the next status/labeling meeting will be held on August 21, 2000

/S/ 7/18/00

Signature, minutes preparer

/S/

Concurrence, Chair

drafted: EDeGuia/08.08.00

cc:

NDA Arch:

HFD-580 Div. File

HFD-580/DEGuia

HFD- 580/SAllen/MMann/DShames/SSlaughter/LKammerman/TRumble/

AParekh/KDavisbruno/RBennett/MRhee/

HFD-510-DWu/YYang

Concurrences: DShames,YYang08.10.00/LKammerman08.11.00

KDavisBruno,SSlaughter08.15.00/RBennett,RKavanagh08.22.00/

MRhee08.23.00

No response received: AParekh,DWu

Final: EDeGuia

Meeting Minutes

FAX

ORIGINAL

CONFIDENTIAL



PART OF THE ARES SERONO GROUP



Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

ORIG AMENDMENT

BSM

Date: 24 July 2000

2

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149

Phone: (301) 827-4260

Fax phone: (301) 827-4267

CC: _____

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

REMARKS: Urgent For your review Reply ASAP Please comment

Dear Freshnie,

Per our conversation this morning regarding the Ovidrel label,

- Tables 2, 4 & 6 relate to the efficacy analysis population (which includes patients who were randomized to receive hCG).
- 5 additional patients from the US study (7927) were treated with hCG but not randomized and were included in the safety analysis population: 1 received Ovidrel 250 mcg and 4 received Profasi. This is stated in Section 12 of the 7927 Study report (Volume 58 of 88, page 102), attached with this fax.

Therefore, if one counts these 5 patients, the statement on Line 266 is accurate and consistent with the figures reported in Table 8 of the PI (Line 270). If one adds the 99 patients in each treatment group from Study 8209 (Table 6) to the figures in Table 8, it confirms the statement that "The safety of Ovidrel was examined in four clinical studies that treated 752 patients of whom 424 received r-hCG following follicular recruitment with Gonadotropin."

Please call me at (781) 681 2267 if you need further clarification. Sincerely,

Debbie

12. SAFETY EVALUATION

All 296 patients who entered the hFSH treatment phase are included in safety evaluations. A total of 280 of these patients received a single dose of hCG including 275 patients who were randomized and received hCG per protocol and five patients who received hCG outside of the protocol, after discontinuation. Of these five patients, four received Profasi® and one received 250 µg r-hCG. In the latter case, the patient was inadvertently administered 250 µg r-hCG without first opening the randomization envelope and thus was judged not to have been randomized. Sixteen of the 296 patients did not receive hCG.

12.1. EXTENT OF EXPOSURE

A total of 275 of the 296 patients treated with FSH went on to receive a single dose of hCG including 94 patients who received 250 µg r-hCG, 89 who received 500 µg r-hCG and 92 who received Profasi®. Five additional patients received hCG outside of the protocol including four patients who received Profasi® and one who received 250 µg r-hCG.

Dosing information is displayed by patient in List 2.1 in Section 16.2.6. Because hCG was administered as a single injection, no tabulations were performed to calculate duration of treatment or total dose.

A total of 296 patients received at least one dose of hFSH during this study. Descriptive statistics for total dose and duration of treatment are displayed by randomization group in Table 27. Median duration of hFSH treatment was 10 days with a range of 6 to 17 days. Median total dose of hFSH administered was 2250 IU with a range of 900 to 6000 IU. The three hCG treatment groups were not different with regard to total dose and duration of FSH treatment. In addition, results for the 21 patients in the non-randomized group were similar to those observed in the hCG-treated patients.

Dosing information is displayed by patient in Lists 1.2 and 1.3 in Section 16.2.6; data listings supporting the tabulations can be found in Section 16.1.9.



ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential

Serono

PART OF THE APES SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 USA
(800) 283-8088
TEL: (781) 982-9000
FAX: (781) 871-6754

July 20, 2000

C O N F I D E N T I A L

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD.20857

ORIG AMENDMENT

134



NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Request for Information: Updated Package Insert

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request by the Agency on July 6, 2000 for a revised draft label which contains clinical information from our Ovulation Induction (OI) Trial (Study 8209). Reference is also made to a request by the Agency on July 18, 2000 to make some revisions to the Pregnancy Category section of the label.

Herewith, please find the revised draft annotated package insert, as requested. For the convenience of the reviewers, the label is provided in both paper and electronic formats. Please note that the following sections have been updated:

- Clinical Studies:** Clinical efficacy information has been added to the label for the Ovulation Induction indication beginning on Line 119. Two tables of efficacy data from the OI study have been inserted in a similar format to those provided for In Vitro Fertilization (IVF). Specifically, Table 6 and Table 7 contain Efficacy Outcomes by Treatment Group and Pregnancy Outcomes by Treatment Group, respectively.
- Warnings / Multiple Births:** Information on live deliveries from OI Study 8209 has been added to this section beginning on Line 209.
- Carcinogenesis, Mutagenesis, Impairment of Fertility:** The following statement has been added to this section of the label per FDA's request beginning on line 254:

4. **Pregnancy:** Per FDA request, line 258 now reads "Pregnancy Category X"

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



ARGENTINA
 AUSTRALIA
 AUSTRIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH-KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential

Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

July 13, 2000

ORIGINAL

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urologic
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection) **NEW CORRESP**
 Letter of Cross Reference

NC

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request from the Division made on May 31, 2000 for a letter of authorization to cross-refer to proposed alternate diluent (Sterile Water for Injection, USP, 1 mL ampule) for use with Ovidrel® manufactured by _____ Accordingly, enclosed is a letter of Authorization which allows FDA to cross-refer to information contained in _____ Type II DMF _____ We wish to inform you that the information contained in DMF _____ held by _____ has not recently been updated. However, information such as specifications and test methods, and product stability can be found in our NDA 21-149 (Volume 11 of 88, page 356-389).

Note that the diluent manufactured by _____ has been approved by FDA and is marketed under Serono NDA 20-378 for Gonol-F® (follitropin alfa for injection). A letter of authorization to cross-refer to NDA 20-378 has been sent under separate cover, as requested.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at (781) 681-2267, or the undersigned at (781) 681-2298.

Yours sincerely,

Pamela Williamson Joyce
 Vice President,
 Regulatory Affairs

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 8, 2000
LLP 7/8/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 21-149)

I have reviewed the financial disclosure information submitted by Serono Laboratories, Inc. in support of NDA 21-149. The documents reviewed were dated November 23, 1999, February 16, and June 28, 2000.

Three studies were conducted to support the safety and efficacy for Ovidrel [choriogonadotropin alfa for injection, recombinant-human chorionic gonadotropin (r-hCG) for injection]. The study numbers and their respective outcome with regard financial disclosure obligations are summarized below:

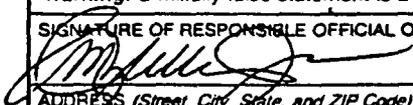
Study No.	Study Status	Financial Disclosure Documentation
7927 ** U.S.	Ongoing as of February 2, 1999	Appropriate documentation; no financial arrangements/proprietary interest
7648 Europe and Israel	Ongoing as of February 2, 1999	Appropriate documentation; no financial arrangements/proprietary interest
8209 Europe and Israel	Ongoing as of February 2, 1999	Appropriate documentation; no financial arrangements/proprietary interest

** 16/93 investigators (17.2%) did not complete the appropriate paper work and return it to the sponsor. This affected approximately 26% of all patients enrolled in this study (7927). The sponsor performed due diligence in regard to contacting these investigators.

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>		Form Approved: OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Serono Laboratories, Inc.		DATE OF SUBMISSION July 5, 2000
TELEPHONE NO. (Include Area Code) (781) 982-9000		FACSIMILE (FAX) Number (Include Area Code) (781) 878-5001
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 Longwater Circle Norwell, MA 02061		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		NDA 21-149
ESTABLISHED NAME (e.g., Proper name, USPI/USAN name) choriogonadotropin alfa	PROPRIETARY NAME (trade name) IF ANY Ovidrel	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) recombinant human chorionic gonadotropin	CODE NAME (If any)	
DOSAGE FORM: lyophilized powder for injection	STRENGTHS: 250 mcg	ROUTE OF ADMINISTRATION: subcutaneous
(PROPOSED) INDICATION(S) FOR USE: Induction of final follicular maturation and early luteinization in infertile women pretreated with FSH as part of an ART program (such as IVF) and embryo transfer.		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER		
REASON FOR SUBMISSION Financial Disclosure Information for Clinical Study 8209		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 1	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION		
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		
IND 48,934		

This application contains the following items: (Check all that apply)		
1. Index		
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))		
4. Chemistry section		
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)		
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)		
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)		
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	Not Applicable	
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)		
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)		
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)		
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))		
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))		
15. Establishment description (21 CFR Part 600, if applicable)		
16. Debarment certification (FD&C Act 306 (k)(1))		
17. Field copy certification (21 CFR 314.50 (k) (3))		
18. User Fee Cover Sheet (Form FDA 3397)		
<input checked="" type="checkbox"/> 19. OTHER (Specify) Financial Disclosure Information for Clinical Study 8209		
CERTIFICATION		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Pamela Williamson Joyce Vice President, Regulatory Affairs	DATE July 5, 2000
ADDRESS (Street, City, State, and ZIP Code) 100 Longwater Circle, Norwell, MA 02061	Telephone Number (781) 982-9000	
<p>Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p> <p>Please DO NOT RETURN this form to this address.</p>		

Attachment C

Financial Disclosure for _____

Study 8209

_____ was the Principal Investigator for site 02 _____ and enrolled 6 patients under his participation in Serono Clinical Trial 8209. This center was the 14th highest enrolling site (out of 19 participating centers), representing 2.5% of patients enrolled. Professor _____ received approximately \$13,056 for equipment purchases for his clinic \ _____ and approximately \$27,417 as a grant to conduct a study on _____”

_____ As the trial design was double-blind and double-dummy, there was no investigator bias.



ARGENTINA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
UK
URUGUAY
USA
VENEZUELA

Confidential

Serono

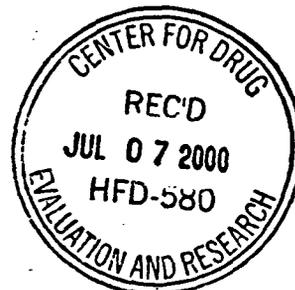
PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

ORIGINAL

July 5, 2000

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urology
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Financial Disclosure for Study 8209

NEW CORRESP

NC

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to recent discussions with the Agency on the Financial Disclosure Information which was submitted in the NDA. Subsequently, it became apparent that Serono inadvertently neglected to submit Financial Disclosure for investigators who participated in Clinical trial 8209 in the original NDA 21-149.

Accordingly, please find the Financial Certification and Disclosure Information in the following Attachments:

- Attachment A: Non-US Investigator List – Financial Certification (Study 8209)
- Attachment B: List of Investigators for Whom Due Diligence Was Performed, but Disclosure was not Obtained
- Attachment C: Financial Disclosure (Form 3455) for one investigator (_____)

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

cc: Ms. Lana Pauls

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



ARGENTINA
 AUSTRALIA
 AUSTRIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential

Serono

PART OF THE ARES SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

June 28, 2000

ORIGINAL

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urology
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Request for Information: Updated Financial
Disclosure for Study 7927

NEW CORRESP

Dear Dr. Allen,

NC

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request made by the Agency on June 26, 2000 for updated Financial Disclosure Information for Clinical Study 7927.

Herewith, please find the information requested in the following Attachments:

- Attachment A: US Investigator List – Financial Certification (Study 7927).
- Attachment B: List of Investigators for Whom Due Diligence Was Performed, but Disclosure was not Obtained

Please note that these documents have been updated to reflect Financial Disclosure from four investigators received subsequent to the submission of NDA 21-149. Additionally, as requested, the number of patients enrolled per center has been added to Attachment B.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
 Vice President, Regulatory Affairs

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
CSO INITIALS	DATE	

cc: Ms. Lana Pauls (fax)



ARGENTINA
 AUSTRALIA
 AUSTRIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH-KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential



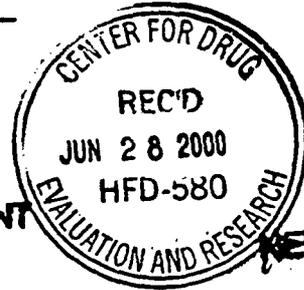
PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

June 27, 2000

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urology
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857

ORIGINAL



ORIG AMENDMENT

BC

NEW CORRESP

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
General Correspondence: Letter from FDA Local District
Regarding Inspection of _____

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a letter from the _____ of FDA to _____ dated April 18, 2000 recommending approval of their sterile water for injection, 1 mL following their assessment in support of our pending original New Drug Application 21-149 for choriogonadotropin alfa.

Herewith, please find in Attachment 1 the aforementioned letter to _____ which was subsequently forwarded to Serono, Inc.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
 Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

DeGuia

JUN 27 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 1/19/2000

DUE DATE: 6/15/2000

OPDRA CONSULT #: 00-0025

TO:

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

THROUGH:

Eufrecina Deguia
Project Manager
(HFD-510)

PRODUCT NAME:

Ovidrel (choriogonadotropin alfa for injection)

MANUFACTURER:

Serono Laboratories, Inc.

NDA #: 21-149

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Ovidrel. See the checked box below.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

DeGuia

Meeting Minutes

Date: June 26, 2000

Time: 11:00 AM – 12:00 PM

Location: PKLN; 17B-43

NDA: 21-149

Drug Name: Ovidrel (choriogonadotropin alfa for injection)

Indication: final follicular maturation and ovulation in _____

Type of Meeting: Status/Labeling Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)

Daniel Shames, M.D., Team Leader, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D., Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Terri Rumble, Chief, Regulatory Project Management Staff, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Du Gong Wu, Ph.D. - Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products
Division of Metabolic and Endocrine Drug Products, (HFD-510)

Yvonne Yang, Ph.D., Chemistry Reviewer, DMEDP, (HFD-510)

Karen Davis-Bruno, Ph.D. - Pharmacologist, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and
Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Eufrecina De Guia, Regulatory Project Manager, DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the Team's review for this pending NDA.

Background: This new NDA was submitted for Assisted Reproductive Technology (ART) and Ovulation Induction (OI) indications. This application is on a 10-month PDUFA review clock and the User Fee goal date is September 24, 2000.

Decisions reached:

Clinical:

- review in progress; there are no problems encountered so far in the review; application looks acceptable from a safety perspective

Chemistry

- review in progress
- bioassay and stability data have been requested from the sponsor
- a list of information requests will be mailed to the sponsor in two weeks

Clinical Pharmacology and Biopharmaceutics

- review in progress
- some information regarding manufacturing lots will be clarified with the Review Chemist

Pharmacology/Toxicology

- review was completed on April 12, 2000
- additional labeling comments will be incorporated in the draft labeling

Statistics

- review not yet assigned

DSI Inspection

- inspection is scheduled for the second week in June; DSI is aware of the goal date

EER

- major inspections are completed; the drug substance manufacturing site in _____ and the drug product manufacturing site in _____ had been recommended by Office of Compliance as acceptable

Microbiology

- review is on-going; expected date of completion of the review will be early August

Labeling

- the draft labeling can be accessed on the N: drive; any initial comments/edits/changes should be made prior to the next status/labeling meeting on July 25, 2000

Additional Comments:

- a request was made by Dr. Shelley Slaughter to have the reviews completed by August 18, 2000 with corrections and sign-off by the Team Leaders by August 25, 2000.

Action Items:

- Chemistry Reviewer to provide comments for the information request letter that need to be sent to the sponsor

/S/

Signature, minutes preparer

/S/

Concurrence, Chair

drafted: EDeGuia/07.07.00

cc:

NDA Arch:

HFD-580 Div. File

HFD-580/DEGuia

HFD- 580/SAllen/MMann/DShames/SSlaughter/LKammerman/TRumble/

AParekh/KDavisbruno/RBennett/MRhee/

HFD-510-DWu/YYang

Concurrences: TRumble07.11.00/MMann,DShames,MRhee,KDavis-

Bruno07.13.00/YYang,DWu07.18.00/LKammerman07.14.00/SSlaughters07.21.00/SAllen08.07.00

Final: EDeGuia08.07.00

Meeting Minutes



ARGENTINA
 AUSTRALIA
 AUSTRIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential

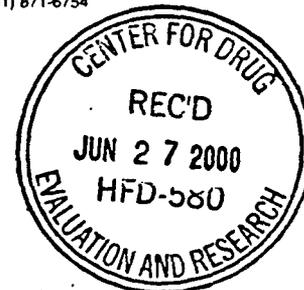
Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

June 26, 2000

ORIGINAL



Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urologic
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857

NDA 21-149
Ovidrel® (choriogonadotropin alfa)
Response to Request for Information: CMC
Bioassay Specification

ORIG AMENDMENT

BC

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request from the Agency for a Bioassay Specification for Ovidrel®. Reference is also made to the Agency 45-Day Filing Meeting held on January 6, 2000, where a request for updated stability data was made.

Accordingly, please find herewith the requested bioassay specification for both r-hCG drug substance and Ovidrel® 250 mcg _____ drug products. The respective stability protocols will be revised to include the proposed specifications. Additionally, updated stability data for the Ovidrel® 250 mcg _____ drug products are provided.

We would be pleased to meet with representatives of the Agency at their convenience to discuss the proposed bioassay specifications.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, at (781) 681 2267 or the undersigned at (781) 681 2298.

Yours Sincerely,

Pamela Williamson Joyce
 Vice President,
 Regulatory Affairs

REVISIONS COMPLETED

CSO ACTION:

LETTER MAIL MEET



ARGENTINA
 AUSTRALIA
 AUSTRIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential



PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

June 16, 2000

ORIGINAL

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urologic
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Letter of Authorization

NEW CORRESP

Dear Dr. Allen,

NC

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request from the Division made on May 31, 2000 for a letter of authorization to cross refer to proposed diluent (Sterile Water for Injection, USP, 1 mL vial) for use with Ovidrel® manufactured by _____ We wish to inform you that _____ no longer provides cross reference to their DMF _____, but instead provides a data package to Sponsors. An information package was provided to Serono Laboratories and can be found in Attachment 1. Additional information such as specifications and test methods, and product stability can be found in our NDA 21-149 (Volume 11 of 88, page 321-355).

Note that the diluent manufactured by _____ has been approved and is marketed under Serono NDA 20-604 for Serostim® [somatropin (rDNA origin) for injection]. A letter of authorization to cross-refer to NDA 20-604 has been sent under separate cover, as requested.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at (781) 681-2267, or the undersigned at (781) 681-2298.

Yours sincerely,

Pamela Williamson-Joyce
 Vice President,
 Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Handwritten initials and date: C/Jan 7-27-00



ARGENTINA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH-KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential

Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

June 16, 2000

ORIGINAL



Susan Allen, M.D., Acting Director,
Division of Reproductive and Urologic
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Letter of Authorization

PL

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a request from the Division made on May 31, 2000 for a letter of cross reference to Serono NDA 20-604 for Serostim® [somatropin (rDNA origin) for injection] approved on August 23, 1996. Please note that the proposed diluent for use with Ovidrel® manufactured by _____ (Sterile Water for Injection, USP, 1 mL vial) has been approved and is marketed under NDA 20-604 with our product, Serostim®.

The purpose of this letter is to authorize the Food and Drug Administration to refer to the chemistry, manufacturing and controls data from NDA 20-604, including information incorporated by reference, in support of a pending NDA 21-149 for Ovidrel® (choriogonadotropin alfa) filed by Serono Laboratories.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, at (781) 681 2267 or the undersigned at (781) 681 2298.

Yours Sincerely,

Pamela Williamson-Joyce
Vice President,
Regulatory Affairs

REVIEW COMPLETED	
CCO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CCO INITIALS	DATE

*WJ
7-27-00*



ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH-KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential

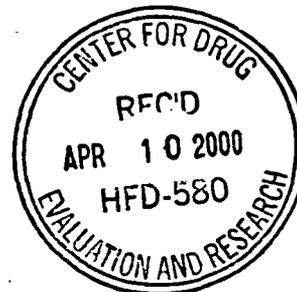
Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

April 7, 2000

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urology
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
120-Day Safety Update Report

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Pursuant to 21 CFR 314.50(d)(5)(vi)(b), herewith please find a 120-Day Safety Update Report. The Analysis of Safety includes all deaths, adverse event-related dropouts and other serious adverse events following Ovidrel® treatment up through the new cut-off date of December 31, 1999. Also included in the summary tables are adverse events from the use of choriogonadotropin alfa in a new indication;

Serono was advised previously by the Division to provide an analysis of the data separately for each indication. The Safety Analysis therefore includes integration of data from three pivotal *In Vitro* Fertilization (IVF) trials (Study 7927, Study 7648 and Study 9073) and Ovulation Induction (OI) trial (Study 8209). The data are then displayed as recombinant hCG (Ovidrel®) versus urinary hCG (Profasi®). Included in this submission are the following:

Volume 1

- Cover letter
- Attachment 1: Letter from United States Adopted Names Council (USAN) dated February 23, 2000 for 'choriogonadotropin alfa' with a written response from Serono noting some errors in the Statement of Adoption
- Attachment 2: Integrated Summary of Safety (120-Day Safety Update)
- Attachment 3: Detailed Table of Contents and floppy disk containing Clinical Trial Report 8209 entitled, "*A phase III, double-blind, double-dummy, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F®)*"



Dr. Susan Allen
NDA 21-149
April 7, 2000
Page 2

Volume 1A

- Attachment 4: SAS datasets (diskette) and Proc Contents for OI Study 8209

Volume 2-3

- Attachment 5: Comparative Bioequivalence Study Report 21443 (which demonstrates bioequivalence between Ovidrel® 500 mcg and Ovidrel® 250 mcg drug products) entitled, *"An open, randomized, 2-way crossover study in healthy male and female volunteers to compare the bioavailability of Ovidrel® given as 1 mL of 500 mcg/mL from the 500 mcg strength vial with 1 mL of 500 mcg/mL from the 250 mcg strength vial"*

Volume 4

- Attachment 6 Population PK/PD Addendum to Study Report 7648 entitled, *"Population analysis of pharmacokinetic and pharmacodynamic data obtained during a phase III, double-blind, double-dummy, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) for inducing final follicular maturation and early luteinization in woman undergoing superovulation with recombinant human Follicle Stimulating Hormone (Gonal-F®) prior to IVF/ET"*

Based on the results of the above study, it is proposed to modify our package insert (line 68 of the annotated draft labeling, original New Drug Application 21-149, volume 2 of 88, page 005) from:

Population pharmacokinetics and pharmacodynamics: _____

to the following:

Population pharmacokinetics and pharmacodynamics: _____

Confidential



Dr. Susan Allen
NDA 21-149
April 7, 2000
Page 3

Volume 5-6

- Attachment 7 *Clinical Trial Report 9073 entitled, "A phase III, double-blind, double-dummy, randomized study to assess the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel[®]) with that of urinary human Chorionic Gonadotropin (Profasi[®]) for inducing final follicular maturation and early luteinization in woman undergoing superovulation with recombinant human Follicle Stimulating Hormone (Gonal-F[®]) prior to IVF/ET and ICSI/ET" which enrolled and treated 84 patients in Australia.*

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact me at (781) 681-2104 or Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267.

Yours sincerely,

Dennis Bucceri
Vice President, Regulatory Affairs USA

cc: Ms. Eufrecina DeGuia (Desk Copy)



ARGENTINA
 AUSTRALIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED. REP. OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH-KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U.K.
 URUGUAY
 USA
 VENEZUELA

Confidential

Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

DEGUIA

February 16, 2000

Susan Allen, M.D., Acting Director,
 Division of Reproductive and Urology
 Drug Products, HFD 580 (Room 17B45)
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Request for Information: List of Clinical Investigators

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a teleconference on February 4, 2000 between E. DeGuia (FDA) and D. DeMuria (Serono) where a request for a list of numbers of patients enrolled per investigator for the clinical studies submitted to the above NDA was made for Dr. R. Bennett's review.

Herewith, please find the information requested in the following Attachments:

- Attachment 1: List of Investigators for Clinical Study 7927
- Attachment 2: List of Investigators for Clinical Study 7648
- Attachment 3: List of Investigators for Clinical Study 8209

For reference and additional information, the list of Clinical Investigators can be found in Section 8A (Volume 38, page 5) and in the individual study reports: 7927 Study Report (Volume 58, page 63, Table 2), 7648 Study Report (Volume 43, page 99, Table 54) and 8209 Study Report dated January 13, 2000 (page 99, Table 56).

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned.

Yours sincerely,

Dennis Bacceri
 Vice President,
 Regulatory Affairs



ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH-KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential

Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

January 31, 2000

*Noted
2/3/00
PCB*
*Noted
fax
8/18/00*

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL



**NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Request for Information: Study 8209 Appendices**

Dear Dr. Allen,

ORIG AMENDMENT

BZ

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a teleconference on January 14, 2000 between E. DeGuia, Dr. L. Kammerman, Dr. S. Slaughter (FDA) and M. Husain (Serono) where a request for a complete list of appendices for the Ovulation Induction (OI) Study (Study 8209) was made.

Herewith, please find the information requested in the following Attachments:

- Attachment 1: Table of Contents for Appendix 16
- Attachment 2: Appendix 16.1.1: Protocol and Protocol Amendments
Clinical Study Protocol (8209): "A phase III, double-blind, double-dummy, randomized, multicentre study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F®)"
- Attachment 3: Appendix 16.1.7: Randomization Scheme and Code
- Attachment 4: Appendix 16.1.9: Documentation of Statistical Methods
- Attachment 5: Appendix 16.2.1: Discontinued Patients
- Attachment 6: Appendix 16.2.3: Patients Excluded from the Efficacy Analysis
- Attachment 7: Appendix 16.4.33: Individual Patient Data Listings – Treatment Completion /Withdrawal (Discontinued for any reason)

Confidential



Susan Allen, M.D.
Ovidrel® NDA 21-149
January 31, 2000
Page Two

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned.

Yours sincerely,

Dennis Bucceri
Vice President,
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE RECEIVED: January 19, 2000
NDA#: 21-149
NAME OF DRUG: Ovidrel (choriogonadotropin alfa for injection)
NDA HOLDER: Serono Laboratories, Inc.

I. INTRODUCTION:

This OPDRA consult is in response to a January 19, 2000 request by the Division of Metabolic and Endocrine Drug Products, to review the proposed proprietary drug name, Ovidrel, regarding potential name confusion with other proprietary/generic drug names. The container label, the carton labeling, and the package insert were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Ovidrel is a sterile lyophilized powder composed of choriogonadotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG), sucrose and phosphoric acid. Choriogonadotropin alfa, the active component of Ovidrel, is an analogue of Luteinizing Hormone (LH) and binds to the LH/hCG receptor of the granulosa and theca cells of the ovary to effect these changes in the absence of an endogenous LH surge. Ovidrel is administered when monitoring of the patient indicates that sufficient follicular development has occurred in response to FSH treatment for ovulation induction. Ovidrel is

pretreated with follicle stimulating hormones as part of an Assisted Reproductive Technology (ART) program such as in vitro fertilization and embryo transfer, or

The dose of Ovidrel must be individualized for each patient. Ovidrel should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. The usual dose is 250 mcg to 500 mcg one day following the last dose of the follicle stimulating agent. Ovidrel is supplied in single dose vials to deliver 250 mcg and 500 mcg r-hCG.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound-alike or

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look-alike Ovidrel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies consisting of written prescription studies and a verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

[The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC)].

1. The panel discussed the following sound-alike/look-alike drug names:

Product Name	Generic name; strength	Usual Dose	Observation
Ovral	50 mcg ethinyl estradiol and 0.5 mg norgestrel tablets	One tablet daily for 21 consecutive days per menstrual cycle. Tablets are then discontinued for 7 days.	
Ovide Lotion	malathion lotion 0.5 %	Apply Ovide Lotion on dry hair in amount just sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally--use no electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs.	
Ovrette	0.075 mg norgestrel tablets	Continuous daily dosage regimen starting on the first day of menstruation.	

*SA = Sound-alike

*LA = Look-alike

The panel identified Ovral, Ovide Lotion, and Ovrette, but concluded that these names do not have the potential for name confusion with Ovidrel, and therefore, the proposed proprietary name is not objectionable.

2. DDMAC – No comments.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

The studies conducted by OPDRA involved ninety-two health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Ovidrel with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Written prescriptions, consisting of (known/unknown) drug products and a prescription for Ovidrel were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, verbal orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

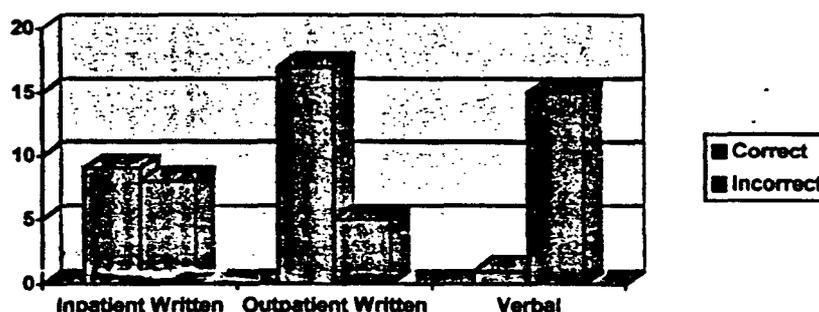
the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Inpatient Written	30	17 (56.7 %)	9 (52.9 %)	8 (47.1 %)
Outpatient Written	31	22 (71 %)	17 (77.3 %)	5 (22.7 %)
Verbal	31	16 (51.6 %)	1 (6.25 %)	15 (93.75 %)
Total	92	55 (59.8 %)	27 (49.1 %)	28 (50.9 %)



C. SAFETY EVALUATOR RISK ASSESSMENT

According to our searches, the proposed proprietary name, Ovidrel, poses no significant safety risk due to the lack of potential confusion with existing product names. In addition, the potential concerns regarding drug marketing and promotion related to the proposed name were also discussed and produced no objections by DDMAC.

According to the results of the verbal and written analysis studies, twenty-seven out of fifty-five [49.1%] participants correctly interpreted Ovidrel. However, the majority of the incorrect responses were misspelled/phonetic variations of the drug name. Moreover, the responses did not overlap with any existing approved drug products. Therefore, there is insufficient evidence at this time to conclude that there is a safety risk of name confusion and to render the proposed proprietary name, Ovidrel, objectionable.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Ovidrel, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container label, carton labeling, and the package insert and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Since this drug must be reconstituted before administration, we recommend revising the established name to read:

OVIDREL™
(Choriogonadotropin Alfa for Injection)

2. We recommend adding the statement, "Rx Only", if space permits.
3. We recommend revising the statement, "_____ " to read:
For Single Use Only - _____
4. We recommend relocating the statement, "For Subcutaneous Injection", from the side to the front of the label.
5. In order to prevent medication errors due to the _____ we recommend differentiating the labels for the two strengths (e.g. different colors, boxing, bolding etc.).

SYRINGE LABEL

We recommend relocating "1 mL" from the side to the front of the label.

B. CARTON LABELING

1. We recommend revising the statement, "After reconstitution with 1 vial of enclosed diluent, product will deliver 250 mcg," to read, "After reconstitution with 1 mL of Sterile Water for Injection, each mL contains 250 mcg of choriogonadotropin alfa..."
2. We recommend relocating the statement, "Rx Only," to the front panel.
3. It is unnecessary to state, "Keep out of reach of children."
4. See comments under CONTAINER LABEL.

C. INSERT LABELING

1. Under the DOSAGE AND ADMINISTRATION SECTION, the reconstitution instruction reads, "...in 1.0 mL Sterile Water for Injection..." Since the use of terminal zeros could cause medication errors, we recommend deleting the terminal zero.
2. Under the HOW SUPPLIED section, we recommend revising the statement, "... _____ " to read:

Ovidrel (choriogonadotropin for injection) is supplied in sterile, lyophilized single dose vials to deliver 250 mcg _____ r-hCG after reconstitution.

D. PACKAGING

IV. RECOMMENDATIONS:

- A. OPDRA does not object to the use of the proprietary name, Ovidrel.
- B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at 301-827-3243.

 /S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

 /S/

 6/27/2006

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA: 21-149

Office Files

HFD-510; DivFiles; Eufrecina Deguia, Project Manager

HFD-510; John Jenkins, Acting Division Director

HFD-042, Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Mary Dempsey, Project Manager, DDRE II, OPDRA (Electronic Only)

HFD-400; Sammie Beam, Project Manager, Medication Errors, OPDRA (Electronic Only)

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

**HFD-002; Mac Lumpkin, Deputy Center Director for Review Management
(Electronic Only)**

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Foreign Marketing History

Ovidrel® is not approved for sale in any foreign country.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Application Integrity Policy (AIP)

This application was not subject to AIP.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Advertising Material

No advertising material has been submitted.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Press Office Notification

The Press Office will be notified upon approval. There will be no Press Release or Talk Paper issued for this product.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Post-marketing Commitments

There are no Phase 4 commitments required for this NDA.

D/F

Teleconference Minutes

Date: January 19, 2000 **Time:** 09:50 – 10:00 AM **Location:** PKLN; 17B-45

NDA: 21-149 **Drug Name:** Ovidrel (choriogonadotropin alfa for injection)

Indication: final follicular maturation _____
Technology (ART) Assisted Reproductive

External Participant: Dr. Murad Husein (Serono Laboratories)

Type of Meeting: Information Request (clinical and Statistical)

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Shelley Slaughter, M.D., Ph.D., Team Leader, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

Eufrecina De Guia, Regulatory Project Manager, DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To request additional information regarding listings and appendices that were missing from the study report for the Ovulation Induction indication.

Background: This new NDA was submitted for Assisted Reproductive Technology (ART) and Ovulation Induction (OI) indications. In the filing meeting on January 6, 2000, it was determined that that the OI study report was not provided. Without the report, the OI indication could not be reviewed.

Discussion Points:

- the study report does not contain a listing of appendices; this is a requirement per the E-3 of the ICH guideline which the report appears to be following; without the list of appendices and their availability upon request, the OI indication can not be reviewed
- there were no filing issues noted for the Assisted Reproductive Technology (ART) indication

Decisions reached:

- the following items were requested from the sponsor:
 - OI study protocol and protocol amendments
 - randomization schemes and codes
 - documentation of statistical methods
 - patient data listings
 - list of discontinued patients

- it was reiterated to the sponsor that all the appendices requested should be received by February 4, 2000 or the OI indication will not be reviewed

Action Items:

- minutes will be sent to the sponsor within 30 days
- sponsor to submit an amendment to NDA with appendices and data as requested

Post-Meeting Addendum: A submission that contained the appendices was received on February 2, 2000. The sponsor was informed by telephone on February 3, 2000 that the submission was acceptable.

 /S/

Signature, minutes preparer

 /S/

/Concurrence, Chair

2/7/00

drafted: EDeGuia/01/28/00

cc:

NDA Arch:

HFD-580/Division File

HFD-580/SSlaughter/LKammerman/TRumble

Concurrences: TRumble02.09.00/LKammerman02.15.00/SSlaughter02.17.00

2.17.00
/S/



ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH-KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential



PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

January 13, 2000

Lisa Rarick, M.D., Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL AMENDMENT

LM



**NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Information Request: Clinical Trial Report
for OI Study 8209**

Dear Dr. Rarick,

Reference is made to NDA 21-149 dated December 24, 1999 and to a subsequent teleconference on January 6, 2000 between Diane Moore and Shelly Slaughter (FDA); Dennis Bucceri, Debbie DeMuria and Murad Husain (Serono Laboratories, Inc.) during the Division Meeting. A request was made to Serono for the Clinical Trial Report for the Ovulation Induction (OI) Study (Study 8209).

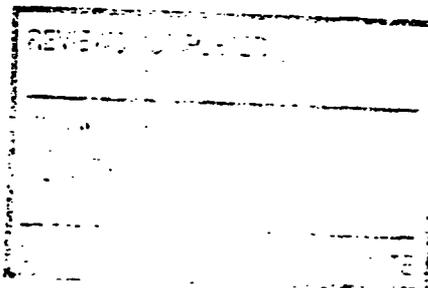
Accordingly, please find in Attachment I the Clinical Trial Report for the OI Study (Study 8209) entitled, "A phase III, double-blind, double-dummy, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F®)".

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned.

Yours sincerely,

Dennis Bucceri
Vice President,
Regulatory Affairs



N-21149

FAX

CONFIDENTIAL

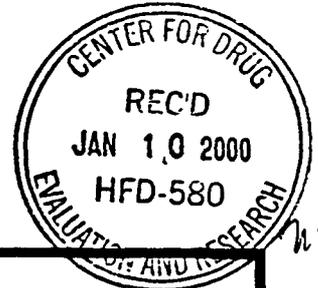
Serono

PART OF THE ARES SERONO GROUP

Date: 07 January 2000

3

Serono Laboratories, Inc.
 100 Longwater Circle
 Norwell, MA 02061



To: Ms. Diane Moore
(HFD-580)

re:

Phone: (301) 827-4260

Fax phone: (301) 827-4267

CC:

From: Debble DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

noted
44
2/22/00

~~NDA SUPPLEMENT~~ BZ

COMMITMENT

REMARKS: Urgent For your review Reply ASAP Please comment

Dear Diane,

As requested, attached please find the replacement page (page 4) to volume 1.2 (Draft Package Insert). Also, please find a copy of page 391 from Volume 1.11 (CMC section) which confirms that the intended formulation for the marketed Ovidrel drug product was the same as that used in clinical trials, both in ~~the EU~~ and in the US. The statement is as follows:

The liquid formulation (used in a Phase I) "was shown to be bioequivalent to the freeze dried formulation used in all subsequent trials and in the marketed product".

Additionally, I would like to confirm that the Clinical Trial Report for the OI study (Study 8209) will be provided by mid next week. The additional stability data will be forthcoming.

Please call me should you need any additional information at (781) 681 - 2267.

Sincerely,

Debbie DeMuria

Debbie DeMuria

noted
1/31
2/24/00

REVIEWS COMPLETED

CSC ACTION:

LETTER N.A.I. MEMO

ED *2-25-00*

CSC INITIALS DATE

OVIDREL 250 µg
Investigational Formula

During the clinical development of the finished product two formulations, a liquid formulation and a freeze-dried formulation, were used.

The liquid formulation was used in phase I clinical development to establish the first pharmacokinetic and pharmacodynamic data in humans.

In trial GF 7014 this formulation was shown to be bioequivalent to the freeze-dried formulation used in all subsequent trials and the marketed product.

The composition of the liquid formulation is detailed hereafter.

One vial of _____ contains:

Name of Ingredient	Unit Formula	Function
Choriogonadotropin alfa	_____	Active ingredient
O-phosphoric acid	_____	_____
Sodium hydroxide (0.1 M)	_____	_____
Water for injection	_____	_____

Meeting Minutes

Date: January 6, 2000

Time: 10:00 - 10:30 AM

Place: Parklawn; Rm. 17B-43

NDA: 21-149

Drug Name: Ovidrel (choriogonadotropin, alfa) 250/500 mcg

Indication: final follicular maturation

technology (ART)

assisted reproductive

Type of Meeting: Filing

Sponsor: Serono

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Susan Allen, M.D., M.P.H. – Medical Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Leslie Furlong, M.D.- Medical Officer, DRUDP (HFD-580)

Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)

Soraya Madani, Ph.D. – DPEII @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Yvonne Yang – Chemist, DNDC II @ HFD-510

Karen Davis-Bruno, Ph.D. – Pharmacologist, DRUDP (HFD-580)

Meeting Objective: To discuss the fileability of the submitted NDA.

Background: Ovidrel is a recombinant chorionic gonadotropin. The precursor drug to this is a urinary-derived chorionic gonadotropin (Profasi). The sponsor

Discussion Items:

- **Clinical**

- the sponsor has performed two assisted reproductive technology (ART) studies: one was a double-blind study, performed in Europe, which compared a subcutaneous administration of 250 mcg of recombinant product with a subcutaneous administration of the urinary-derived product; the other study was an open-label study conducted in the U.S. comparing 250 mcg and 500 mcg subcutaneous doses of the recombinant product with Profasi, 10,000 International Units (IU); the sponsor plans to submit results from an ovulation induction (OI) study which is currently being performed using both drug products.

Meeting Minutes – January 6, 2000

- no protocol has been submitted for the OI study
- the European study compared the recombinant product to a 5000 IU dose of the urinary-derived product based on historical doses of the urinary-derived product, whereas, the U.S. study compared the recombinant product to 10,000 IU doses of the urinary-derived product
- Chemistry
 - the sponsor has submitted data from — scale batches requesting 24-month expiration dating at 25°C; they also have — full scale batches with — stability data at 25°C, 40°C and 50°C; in order to obtain a 2-year expiration date for the product, minimal stability data for — at 25°C from — batches should be submitted for review before the PDUFA deadline
 - submission of additional stability data after seven months (for a 10-month review clock) or nine months (for a 12-month review cycle) could be considered a major amendment to the NDA and delay the review by three additional months
- Pharmacology
 - Fileable
- Clinical Pharmacology and Biopharmaceutics
 - additional information will be requested regarding protein binding and mass balance issues
 - if the drug used in the clinical trials is not the same as the to-be-marketed formulation, a bridging study would be needed
- Statistics
 - the pregnancy rates in the ART studies appear to be similar for the compared products in the submitted studies
 - the NDA does not include a study report for the OI indication; therefore, this indication is not fileable
- Regulatory
 - the sponsor requested a priority review for this NDA

Decisions:

- Clinical
 - fileable for the ART indication; however, the NDA cannot be reviewed for the OI indication unless complete results from the OI study are submitted before the filing deadline
- DSI
 - proposed clinical inspection sites should be submitted to the Division of Scientific Investigations
- Chemistry
 - fileable
 - additional information regarding the characterization of the glycoprotein will be requested during the review cycle
 - additional stability data should be submitted within seven months of the submission date
 - a tradename review will be sent to OPDRA
 - a microbiology review has been requested
 - manufacturing site inspection(s) should be requested
- Clinical Pharmacology and Biopharmaceutics
 - fileable; it must be clarified whether the formulation studied in the clinical trials is the same as the to-be-marketed formulation
- Regulatory
 - this NDA does not warrant a priority review

Action items

Item :	Responsible Person :	Due Date:
• request clarification from sponsor for timing of OI study submission	Ms. Moore	1 week
• clarify with sponsor whether the drug studied in the clinical trials is the same as the to-be-marketed product (see below)	Ms. Moore	ASAP
• clarify the proposed timing for additional stability data	Ms. Moore	2 weeks

/S/

Signature, recorder

2/11/00

/S/

Signature, Chair

2/14/00

Post-Meeting Addendum: During a teleconference on December 6, 1999, with Mr. Dennis Bucceri, from Serono, it was clarified that the drug studied in the clinical trials is the same as the proposed to-be-marketed drug. It was also clarified that the results from the OI trial would be submitted within two weeks and the stability data would be forthcoming (see attached telefacsimile). The sponsor plans to submit stability data within two months of NDA submission.

On January 14, 2000, upon review of the submitted OI study report, the Biometrics discipline determined that the OI indication is not reviewable because the OI study protocol, protocol amendments and listing of appendices are not included in the submission. Although the submitted report indicated "appendices are available upon request," the submission contained neither a list of the appendices nor the appendices themselves. Some items (e.g., randomization code, analyses by center), critical to a review of the OI study, presumably, are located in the appendices.

drafted: dm/01.12.00/N21149FM1600.doc

cc:

HFD-580

HFD-580/MMann/SSlaughter/RBennett/SUAllen/ENevius/LKammerman

HFD-/ FHoun

Concurrences:

KColangelo 1.12.00/LFurlong 1.13.00/RBennett, SMadani 1.14.00

SAllen, KDavis-Bruno 1.18.00/ LKammerman 1.20.00, 2.7.00/YYang 1.21.00/MRhee 1.24.00

SSlaughter 1.27.00/AParekh 2.11.00

Minutes of Teleconference

Date: January 6, 2000

Time: 12:50 - 1:00 PM

Place: Parklawn; Rm. 17B-43

NDA: 21-149

Drug Name: Ovidrel (chyoriogonadotropin, alfa) 250/500 mg

Indication: final follicular maturation and ovulation in women undergoing ovulation induction and oocyte maturation prior to fertilization in women undergoing assisted reproductive technology (ART)

Type of Meeting: Information request

External Constituent: Serono Laboratories, Inc.

FDA Lead: Dr. Shelley Slaughter

External Participant Lead: Mr. Dennis Bucceri

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Shelley Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

External Participants:

Dennis Bucceri, R.Ph. – Executive Director, Regulatory Affairs Serono Laboratories

Debbie DeMuria, Pharm. D. - Senior Regulatory Associate, Serono Laboratories

Murad Husain - Associate Director, Regulatory Affairs

Meeting Objective: To request clarification for outstanding questions from filing meeting held on January 6, 2000 for this NDA.

Background: Filing meeting was held on January 6, 2000.

Discussion Items:

- the sponsor clarified that the drug studied in the clinical trials is the same as the to-be-marketed product
- the sponsor expects to have a final report on the ovulation induction (OI) study by the end of January 2000
- additional _____ of stability data will be submitted within the next two weeks; the sponsor will confirm the dates of the reports with the FDA Project Manager

Decisions:

- in order to file NDA 21-149 for the OI indication, the study report must be submitted to the NDA by January 14, 2000; otherwise, the NDA will be filed for the ART indication only

Desina

NDA 21-149

NOV 30 1999

Serono Laboratories, Inc.
Attention: Dennis J. Bucceri, R.Ph.
Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

Dear Dr. Bucceri:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ovidrel (recombinant human chorionic gonadotropin alfa) for injection, 250 mcg
Therapeutic Classification:	Standard (S)
Date of Application:	November 23, 1999
Date of Receipt:	November 24, 1999
Our Reference Number:	NDA 21-149

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 23, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 24, 2000 and the secondary user fee goal date will be November 24, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

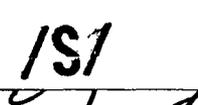
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Refer to Attachment A - U.S. Investigators	
	Refer to Attachment B - non-U.S. Investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Thomas A. Lang	TITLE Sr. Vice President, Strategic Prod. Development
FIRM/ORGANIZATION Serono Laboratories, Inc., Norwell, Massachusetts	
SIGNATURE 	DATE November 23, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Attachment A

**U.S. Investigator List
Financial Certification**

Investigator/ Subinvestigator	Center Number	Country	Comment
	11	U.S.	
	10	U.S.	
	4	U.S.	
	11	U.S.	
	10	U.S.	
	19	U.S.	
	12	U.S.	
	3	U.S.	
	9	U.S.	
	9	U.S.	
	9	U.S.	
	18	U.S.	
	10	U.S.	
	2	U.S.	
	1	U.S.	
	2	U.S.	
	14	U.S.	
	2	U.S.	confirmed in writing that she had no involvement in this study
	4	U.S.	
	19	U.S.	
	14	U.S.	
	6	U.S.	
	4	U.S.	
	2	U.S.	
	3	U.S.	
	2	U.S.	
	11	U.S.	
	18	U.S.	
	2	U.S.	
	7	U.S.	
	6	U.S.	

Attachment A

**U.S. Investigator List
Financial Certification**

	15		U.S.	
	19		U.S.	
	7		U.S.	
	11		U.S.	
	17		U.S.	
	15		U.S.	
	8		U.S.	
	15		U.S.	
	11		U.S.	
	1		U.S.	
	2		U.S.	
	20		U.S.	
	9		U.S.	
	11		U.S.	
	10		U.S.	
	4		U.S.	
	15		U.S.	
	8		U.S.	
	12		U.S.	
	13		U.S.	
	5		U.S.	
	3		U.S.	
	5		U.S.	
	13		U.S.	
	6		U.S.	
	6		U.S.	
	7		U.S.	
	8		U.S.	
	4		U.S.	
	16		U.S.	
	2		U.S.	
	2		U.S.	
	10		U.S.	
	17		U.S.	
	13		U.S.	
	4		U.S.	
	4		U.S.	

Attachment A

**U.S. Investigator List
Financial Certification**

	7		U.S.	
	10		U.S.	
	14		U.S.	
	15		U.S.	
	18		U.S.	
	20		U.S.	
	19		U.S.	
	13		U.S.	
	3		U.S.	
	6		U.S.	
	20		U.S.	confirmed in writing that he had no involvement in this study

Attachment B

**Non-U.S. Investigator List
Financial Certification**

Investigator/Subinvestigator	Center Number	Country
	9	Israel
	2	France
	1	France
	5	NL
	9	Israel
	4	Germany
	3	Germany
	5	NL
	4	Germany
	8	Italy
	2	France
	8	Italy
	7	UK
	1	France
	5	NL
	7	UK
	3	Germany
	6	Sweden
	6	Sweden

Attachment C

**List of Investigators
for whom Due Diligence was Performed but Disclosure was Not Obtained**

Subinvestigator	Center Number	Country	Reason Information Not Obtained
	6	U.S.	No forwarding address
	6	U.S.	No forwarding address
	18	U.S.	No response
	6	U.S.	No forwarding address
	6	U.S.	No forwarding address
	18	U.S.	No forwarding address
	13	U.S.	No forwarding address
	10	U.S.	No response
	6	U.S.	No response
	5	U.S.	Deceased
	11	U.S.	No response
	10	U.S.	No response
	2	U.S.	No forwarding address
	19	U.S.	No forwarding address
	11	U.S.	Retired 12/31/98
	6	U.S.	No forwarding address
	16	U.S.	No forwarding address



ARGENTINA
 AUSTRALIA
 BELGIUM
 BRAZIL
 CANADA
 COLOMBIA
 FED REP OF RUSSIA
 FRANCE
 GERMANY
 ISRAEL
 ITALY
 JAPAN

MEXICO
 NETHERLANDS
 PORTUGAL
 SINGAPORE
 SOUTH KOREA
 SPAIN
 SWEDEN
 SWITZERLAND
 UKRAINE
 U K
 URUGUAY
 USA
 VENEZUELA

Confidential

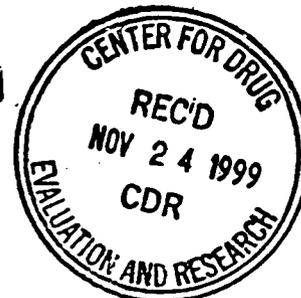
(Sero)

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
 100 LONGWATER CIRCLE
 NORWELL, MA 02061 / USA
 (800) 283-8088
 TEL (781) 982-9000
 FAX (781) 871-6754

November 23, 1999

Lisa Rarick, M.D., Director,
 Division of Reproductive and Urology
 Drug Products, HFD 580
 Center for Drug Evaluation and Research
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



**NDA 21-149
 Ovidrel® (choriogonadotropin alfa for injection)
 New Drug Application**

Dear Dr. Rarick,

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50 Sero Laboratories, Inc. herewith submits an original New Drug Application for Ovidrel® [choriogonadotropin alfa for injection, recombinant-human chorionic gonadotropin (r-hCG) for injection]. The Ovidrel® NDA has been preassigned the number NDA 21-149. As required, a check for the application fee in the amount of \$272,282 has been submitted. A copy of the cover letter and check is enclosed in Volume 1 of 88 (archival copy only).

Ovidrel® is a pharmaceutical preparation of human chorionic gonadotropin of recombinant origin. Human chorionic gonadotropin (hCG) is a glycoprotein from the same family as the pituitary gonadotropins (human follicle stimulating hormone, human luteinizing hormone) and human thyroid stimulating hormone. It is composed of a single α -subunit of 92 amino acids (common to all members of the glycoprotein hormone family) and a target specific β -subunit of 145 amino acids. It is structurally close to human luteinizing hormone (hLH), with which it shares 80% homology in the β -subunit, which is functionally reflected by the fact that both hormones bind to the same cell surface receptor.

Chorionadotropin alfa, being physico-chemically identical to native hCG, would therefore be anticipated to be clinically equivalent to urinary hCG (u-hCG) in inducing final follicular maturation and ovulation in women undergoing ovulation induction, and to induce follicle and oocyte maturation prior to fertilization in women undergoing Assisted Reproductive Technology (ART) for the treatment of infertility.

Chorionadotropin alfa is produced by recombinant DNA technology and is formulated for use by subcutaneous injection. The drug product is available as a lyophilized powder in vials containing 285 μ g r-hCG with accompanying diluent to deliver 250 mcg and 285 μ g r-hCG, respectively. Ovidrel® is intended to replace urinary hCG products, such as Profasi®, which is marketed by Sero. The possibility of subcutaneous administration offers the patient

Lisa D. Rarick, M.D.
Ovidrel® NDA 21-149
November 23, 1999
Page Two

the convenience over intramuscular injections of urinary hCG. Further, the recombinant product is significantly more pure than the urinary counterpart; allows more consistent manufacturing and tighter specifications; and its supply is assured, reliable and safe, all of which are significant improvements over the urinary derived product. Accordingly, Serono respectfully requests priority review of the New Drug Application for Ovidrel®.

Ovidrel® was investigated clinically under IND 48,934 submitted on September 29, 1995. In clinical pharmacology studies where Ovidrel® was compared to Profasi®, the pharmacokinetic profile of recombinant hCG has been shown to be similar to that of urinary hCG. Because of the similarities in metabolism and pharmacological action, it is reasonable to conclude that Ovidrel® is also effective in the female infertility indications for which Profasi® is currently prescribed. Therefore, the clinical development of Ovidrel® has focused on demonstrating therapeutic equivalence to Profasi® for the treatment of infertile women seeking pregnancy.

As of the data cut-off for this application, Serono has completed the clinical phase and data analysis of two randomized, controlled clinical trials of Ovidrel® for the induction of final follicular maturation and early luteinization in women undergoing superovulation prior to *in vitro* fertilization and embryo transfer (IVF/ET). These studies, which are described below, were conducted under the principles of Good Clinical Practice (GCP) in the United States and in Europe and Israel.

Study 7927, (A phase III, open, comparative, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin, administered subcutaneously, with that of urinary human Chorionic Gonadotropin (Profasi®), administered intramuscularly, for inducing final follicular maturation and early luteinization in women undergoing superovulation with highly-purified human Follicle-Stimulating Hormone (Metrodin XP™; Fertinex®) prior to IVF/ET) enrolled 297 patients and was carried out at 20 medical centers in the US.

Study 7648, (A phase III, double-blind, double-dummy, randomized, multicentre study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin with that of urinary human Chorionic Gonadotropin (Profasi®) for inducing final follicular maturation and early luteinisation in women undergoing superovulation with recombinant human Follicle Stimulating Hormone (Gonal-F®) prior to IVF/ET) was conducted in Israel and 6 European countries. A total of 205 patients were enrolled at 9 university centers.

A third study, Study 8209, (A phase III, double-blind, double-dummy, randomized, multicentre study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F®)), is ongoing in Israel and Europe. A total of 234 patients have been enrolled at 18 centers.

Lisa D. Rarick, M.D.
 Ovidrel® NDA 21-149
 November 23, 1999
 Page Three

Serono has conducted the third study (Study 8209) to confirm the safety and efficacy of Ovidrel® in the Ovulation Induction (OI) indication. This OI effect of hCG with FSH has been clearly demonstrated clinically in the approved NDA for Profasi® and, for r-hCG, in the ART studies to be submitted in this Ovidrel® NDA. It is therefore, reasonable to conclude that r-hCG is also effective with FSH for the OI indication in anovulatory, infertile women who desire pregnancy and in whom the cause of anovulation is secondary and not due to primary ovarian failure. A full and final report for Ovidrel® in the OI indication will follow shortly after this submission for Ovidrel®.

The NDA consists of 88 volumes. The breakdown of these volumes is as follows:

- Volume 1: Cover letter, FDA Form 356h, FDA Form 3454 with Investigator List for Financial Disclosure, Patent Information (Item 13), Patent Certification (Item 14), Debarment Certification (Item 16), Field Copy Certification (Item 17), User Fee Cover Sheet: FDA Form 3397 (Item 18), Statement of Market Exclusivity (Item 19) and Pediatric Use statement.
- Volume 2: Application Summary, Draft Labeling (Item 2), Overall NDA Index (Item 3) and Reviewer's Guide.
- Volumes 3-13: Item 4 – Chemistry, Manufacturing, and Controls Information
- Volumes 14-30: Item 5 – Nonclinical Pharmacology and Toxicology
- Volumes 31-37: Item 6 – Human Pharmacokinetics and Bioavailability
- Volumes 38-71: Item 8 – Clinical Data
- Volumes 70-76: Item 10 – Statistical Methodology
- Volumes 77-84: Item 11 – Case Report Tabulations
- Volumes 85-88: Item 12 – Case Report Forms

Please note that the product is produced by _____ The summary of the validation of _____ operations is contained in Item 4. Please also note that the Environmental assessment contained in this application was prepared pursuant to 21 CFR 25.31(a), whereby

_____ and therefore claims categorical exclusion.

For convenience of the reviewers, a Reviewer's Guide and copies of the NDA summary which contains a summary of the Integrated Summary of Safety and Efficacy are also provided at the beginning of each Technical Section. In accordance with 21 CFR 314.50(l)(3), an identical field copy of the Chemistry, Manufacturing and Controls section of this NDA, a summary of the NDA application, and a copy of the Form 356 application form have been submitted simultaneously to the Boston District Office of the FDA. The undersigned hereby certifies that the copy submitted to the district office is a true copy of the above-mentioned sections of application 21-149.

Lisa D. Rarick, M.D.
Ovidrel® NDA 21-149
November 23, 1999
Page Four

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned.

Yours sincerely,



Dennis Bucceri
Vice President,
Regulatory Affairs



ARGENTINA
AUSTRALIA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED. REP. OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential



PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

October 18, 1999

Mellon Bank
Three Mellon Bank Center
27th floor (FDA 360909)
Pittsburgh, PA .15259-0001

Dear Sir/Madam:

Enclosed please find check 37912 in the amount of \$272,282 for Users Fees related to the following original New Drug Application (NDA) which we are submitting to the Division of Reproductive and Urologic Drug Products, US Food and Drug Administration pursuant to Section 351 of the Public Health Service Act.

1. **Company Name and Address:**

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

2. **Contact Person and Phone Number:**

Dennis Bucceri
Tel: (781) 982-9000

3. **Application:** Original NDA for Ovidrel® (choriogonadotropin alfa) injection.

4. **User Fee Number:** 3756

The original NDA contains clinical data generated to support the proposed indication.

Sincerely,

Dennis Bucceri
Vice President, Regulatory Affairs



ARGENTINA
AUSTRIA
BELGIUM
BRAZIL
CANADA
COLOMBIA
FED REP OF RUSSIA
FRANCE
GERMANY
ISRAEL
ITALY
JAPAN

MEXICO
NETHERLANDS
PORTUGAL
SINGAPORE
SOUTH-KOREA
SPAIN
SWEDEN
SWITZERLAND
UKRAINE
U.K.
URUGUAY
USA
VENEZUELA

Confidential



Serono

PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

September 30, 1999

Dr. Duu-Gong Wu
Chemistry Reviewer
Division of New Drug Chemistry II @
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



Ovidrel® (choriogonadotropin alfa for injection)
NDA 21-149
CMC Preview

Dear Dr. Wu,

OCT 1 1999

Reference is made to our planned New Drug Application for Ovidrel® (choriogonadotropin alfa for injection) 250 mcg and ~~_____~~ NDA 21-149. Serono plans to submit this NDA shortly.

In anticipation of the receipt of this NDA for review, you suggested that we provide to you a copy of the proposed specifications, a brief description of the test methods that will be included in the NDA for the drug products and available stability data for the drug products. You also asked that we provide information concerning the reference standard. This information is enclosed as follows:

- Proposed Specifications for Ovidrel® 250 mcg
- Proposed Specifications for Ovidrel® ~~_____~~
- Justification of Test Methods and Specifications for Ovidrel® 250 mcg
- Justification of Test Methods and Specifications for Ovidrel® ~~_____~~
- Batch Analysis Data for Ovidrel® 250 mcg
- Batch Analysis Data for Ovidrel® ~~_____~~
- Stability Data for Ovidrel® 250 mcg
- Stability Data for Ovidrel® ~~_____~~ will be included in the NDA
- Reference Standard Information

We have enclosed the justification for the tests and specifications. However, we want to remind you that the specifications may need to be refined as we gain more experience and accumulate more data. As you explained during a recent telephone conversation, we are providing this information to you so that you can determine whether there might be things that stand out and that we might need to address further in the NDA. We realize that any comments you might provide will not be based on a complete review but will be to alert us to potential questions that may arise during the full review of the NDA.

Confidential



Dr. Duu-Gong Wu
Ovidrel® CMC Preview
NDA 21-149
Page Two

We appreciate your willingness to look this information over and provide comments. Please do not hesitate to call me with any questions or for clarification. My telephone number is:
781-681-2104

Sincerely,

A handwritten signature in black ink, appearing to read "D. Bucceri".

Dennis J. Bucceri,
Executive Director, Regulatory Affairs

NDA EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-149</u> Drug <u>Ovidrel®</u> Applicant <u>Serono Laboratories</u>	
(choriogonadotropin alfa for injection)	
RPM <u>Eufrecina DeGuia</u>	Phone <u>301-827-4260</u>
<u>505(b)(1)</u> 505(b)(2) Reference listed drug _____	
Fast Track	Rolling Review
	Review priority: <u>(S)</u> P
Pivotal IND(s) <u>IND 48,934</u>	
Application classifications: Chem Class <u>3S</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: <u>Primary Sept. 24, 2000</u> Secondary <u>Nov. 4, 2000</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
User Fee Waiver (attach waiver notification letter)
User Fee Exemption

- ◆ Action Letter..... (AP) AE NA

- ◆ Labeling & Labels (including Final Label)

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling?	<u>Yes</u> (include review) No
Immediate container and carton labels	X
Nomenclature review	X

- ◆ Application Integrity Policy (AIP) A pPLICANT is on the AIP. This application is is not on the AIP.

Exception for review (Center Director's memo).....	N/A
OC Clearance for approval.....	N/A

◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review)	Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	N/A
◆ Was Press Office notified of action (for approval action only)?.....	Yes No
Copy of Press Release or Talk Paper.....	N/A
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	X
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	
Disclosable information – indicate where review is located (Action Package).....	X
◆ Correspondence/Memoranda/Faxes	X
◆ FDA Correspondence	
◆ Minutes of Meetings	X
Date of EOP2 Meeting <u>No meeting was held</u>	
Date of pre NDA Meeting <u>No meeting was held</u>	
Date of pre-AP Safety Conference <u>No meeting was held</u>	
◆ Advisory Committee Meeting	N/A
Date of Meeting	N/A
Questions considered by the committee	N/A
Minutes or 48-hour alert or pertinent section of transcript	N/A
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	X
◆ Clinical review(s) and memoranda	X

Continued

◆ Safety Update review(s)	_____	X
◆ Pediatric Information		
Waiver partial waiver (the rationale for waiver is in Action Pkg) D e f e r r e d	_____	X
Pediatric Page.....	_____	X
Pediatric Exclusivity requested? D e n i e d G r a n t e d N o t A p p l i c a b l e		
◆ Statistical review(s) and memoranda	_____	X
◆ Biopharmaceutical review(s) and memoranda.....	_____	X
◆ Abuse Liability review(s)	_____	N/A
Recommendation for scheduling	_____	N/A
◆ Microbiology (efficacy) review(s) and memoranda	_____	N/A
◆ DSI Audits	_____	X
Clinical studies bioequivalence studies	_____	X

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ CMC review(s) and memoranda	_____	X
◆ Statistics review(s) and memoranda regarding dissolution and/or stability	_____	N/A
◆ DMF review(s)	_____	N/A
◆ Environmental Assessment review/FONSI/Categorical exemption	_____	N/A
◆ Micro (validation of sterilization) review(s) and memoranda	_____	X
◆ Facilities Inspection (include EES report)		
Date completed <u>8-21-2000</u>	Acceptable	Not Acceptable
◆ Methods Validation	Completed	Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Pharm/Tox review(s) and memoranda	_____	X
◆ Memo from DSI regarding GLP inspection (if any)	_____	N/A

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A
- ◆ Integrated Summary of Safety (ISS)..... X
- ◆ Integrated Summary of Effectiveness (ISE) X